PATENT SPECIFICATION (11) 1327591

1327591

NO DRAWINGS

(21) Application No. 56527/70 (22) Filed 27 Nov. 1970

(31) Convention Application No. 97310 (32) Filed 4 Dec. 1969 in

(33) Japan (JA)

(44) Complete Specification published 22 Aug. 1973

(51) International Classification A61K 9/00

(52) Index at acceptance

A5B 753 75Y 764

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(54) PROCESS FOR THE PREPARATION OF THE SUSPENSION OF MICROCRYSTALS OF CHLORAMPHENICOL PALMITATE

(71) We, YAMANOUCHI PHARMACEUTICAL CO. LTD., a Japanese Company of No. 5—1, Nihonbashi-Honcho, 2-chome, Chuo-ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a process for the preparation of a suspension of fine crystals of chloramphenical palmitate.

Since chloramphenical palmitate does not have a bitter taste, it is suitable for oral administration but since it is sparingly soluble in water, it is used as a suspension thereof. The chloramphenical palmitate orally administrated is hydrolyzed in an intestinal tract to form chloramphenical, which is absorbed at the intestinal tract.

If the shape or the size of the crystals of chloramphenical palmitate is inadequate, a homogenous and stable suspension of chloramphenicol palmitate cannot be obtained, and the hydrolysis of the chloramphenicol palmitate does not proceed smoothly in the intestinal tract. Thus, in such a case, an effective blood level of chloramphenical cannot be obtained.

Three kinds of crystals of chloramphenicol palmitate are known, that is a thermally stable A-type crystal (also called "β-form") prepared by cooling slowly a solution of chloramphenicol palmitate in a solvent such as methanol or molten chloramphenical palmitate, a thermally unstable B-type crystal (also called "α-form") prepared by cooling rapidly a solution of chloramphenical palmitate or molten chloramphenical palmitate, and a thermally most unstable amorphous type prepared by cooling the solution or the molten compound more rapidly than for the production of the B-type crystal (cf.; FDA Regulation; *21*, (1) 205; Yakugaku Zasshi, *81*, 755—767 (1961), Takamine Kenkyusho Nenpo (Annual Report of Takamine Research Institute), *11*, 84—88, and Japanese Patent Publication No. 5798/'60).

Among the three types of crystal, the A-type crystal of chloramphenical palmitate is thermally stable and hence its solubility and rate of solution in water is low. Accordingly, the crystal is less hydrolyzed in the intestinal tract, the absorption of chloramphenicol at the intestinal tract is less, and hence the effective blood level is not increased. Furthermore, even if the crystal is finely pulverized, it is impossible to reduce the size of the crystal below about 5 microns and the effective blood level is scarcely increased.

Amorphous chloramphenicol palmitate is thermally very unstable and hence cannot be used for practical purposes.

On the other hand, since the B-type crystal of chloramphenical palmitate is thermally unstable as compared with the A-type crystal, the solubility thereof in water is high and the rate of solution is high. Accordingly, the B-type crystal is readily hydrolyzed in an intestinal tract and hence chloramphenical is well absorbed at the intestinal tract and the effective blood level becomes high.

However, the B-type crystal prepared in a conventional manner, e.g. by the method disclosed in the specification of Japanese Patent Publication No. 5798/60 and in Chem. Abstr. 55 5878F (1961) in which the B-type crystal is prepared by dissolving chloramphenicol palmitate in a hydrophilic organic solvent and rapidly cooling the solution, is not sufficiently fine and hence it is difficult to prepare a suspension of these crystals. The B-type crystal obtained in such a conventional manner may be reduced in size by conventional method such as pulverization to facilitate suspension thereof, but the finest size of crystal obtainable in this way is about 2—3 microns. The crystals of this fineness are still not rapidly

hydrolyzed in the intenstinal tract and hence a sufficiently effective blood level cannot be obtained.

The present invention provides a process for the preparation of a suspension of fine crystals of chloramphenical palmitate which comprises mix-melting chloramphenicol palmitate and 3—10%, by weight based on the chloramphenicol palmitate of at least one nonionic surface active agent selected from polyoxyethylene (n=15—30) higher fatty acid (C_{12}—C_{18}) esters, polyoxyethylene (n=10—25) sorbitan higher fatty acid (C_{12}—C_{18}) esters, polyoxyethylene (n=10—20) polyoxypropylene (m=1—4) higher alcohol (C_{12}—C_{18}) ethers, polyoxyethylene (n=15—30) alkyl (C_8—C_{10}) aryl ethers, and polyoxyethylene (n=50—80) hardened castor oil where n and m are as herein defined, solidifying the molten mixture by quenching it, and dispersing the solidified mixture in an aqueous suspension medium by means of a colloid mill. By this process, a suspension of the very fine B-type crystal (less than 0.5 microns) of chloramphenicol palmitate can be produced.

It is impossible to obtain a suspension of such fine crystals of chloramphenicol palmitate by melting chloramphenicol palmitate, solidifying it by quenching, and then dispersing the solidified compound in a suspension medium or a suspension medium containing a surface active agent.

The fact that a satisfactory suspension of very fine crystals of chloramphenical palmitate can be obtained by the process of this invention is thus unexpected.

Since the crystals of chloramphenicol palmitate in the suspension obtained by the process of this invention are much finer than those obtained by pulverizing the B-type crystal in a conventional manner, they provide on oral administration an effective blood level higher than that given by a conventional suspension.

The surface active agents used in this invention are selected from polyoxyethylene (n=15—30) higher fatty acid (C_{12}—C_{18}) esters such as polyoxyethylene stearic acid ester; polyoxyethylene (n=10—25) sorbitan higher fatty acid (C_{12}—C_{18}) esters such as polyoxyethylene sorbitan monostearic acid ester, polyoxyethylene sorbitan monooleic acid ester, and polyoxyethylene sorbitan monopalmitic acid ester; polyoxyethylene (n=10—20) polyoxypropylene (m=1—4) higher alcohol (C_{12}—C_{18}) ethers such as polyoxyethylene polyoxypropylene cetyl alcohol ether; polyoxyethylene (n=15—30) alkyl (C_8—C_{10}) aryl ethers such as polyoxyethylene nonylphenyl ether; and polyoxyethylene (n=50—80) hardened castor oil. As herein defined, n represents the mean degree of polymerization of ethyleneoxide and m the mean degree of polymerization of propyleneoxide.

As the suspension medium, there are illustrated water, an aqueous solution of sodium carboxymethyl cellulose and an aqueous solution of methyl cellulose. An attrition type colloid mill is suitably used as the colloid mill in this invention and a typical colloid mill of such type is a Premier-type colloid mill.

According to one embodiment of this invention, chloramphenicol palmitate and the nonionic surface active agent are mix-melted by heating, the molten mixture is then solidified by being quenched to provide a waxy solid material, the waxy solid material is pulverized by, for example, a mortar, the pulverized material is added to the suspension medium, and after heating if necessary, the mixture is dispersed by means of a colloid mill.

The quenching of the molten mixture is preferably conducted by cooling it rapidly to temperatures of lower than 10°C. In the case when the suspension is heated for processing by the colloid mill, it is preferable to heat to 30—70°C, most preferably 40—60°C.

The process of this invention can be practiced by adding the molten mixture directly into an aqueous suspension medium which has been cooled, preferably to a temperature of lower than 5°C, and then dispersing the mixture by means of a colloid mill.

The suspension of chloramphenicol palmitate obtained by the process of this invention may include conventional additives, for example, a saccharose such as sucrose, glucose, or levulose; a perfume such as a strawberry oil, cherry essence or silk flavor; and a preservative such as p-hydroxybenzoic acid methyl ester or p-hydroxybenzoic acid propyl ester. Such additives may be added to the suspension, or to the suspension medium before the solidified mixture is added thereto.

The invention is described by the following examples although the invention shall not be limited to them.

Example 1

A mixture of 60.0g of chloramphenicol palmitate and 3.0g of polyoxyethylene (n=20) sorbitan stearate was melted and the molten mixture was quenched to 8°C to provide solid material which was pulverized by means of a mortar and added to 1 liter of water. The aqueous mixture was heated to 50°C and then dispersed by means of an attrition type colloid mill to provide a suspension of fine crystals of chloramphenicol palmitate having a size of less than 0.5 microns.

Example 2

A mixture of 60.0g of chloramphenicol palmitate and 2.7g of polyoxyethylene (n=25) stearate was melted and the molten mixture was quenched to 5°C to provide a solid material, which was pulverized in a mortar and added to 1 liter of water. The aqueous mixture was heated to 55°C and then dispersed by means of a colloid mill to provide a sus-

pension of fine crystals of chloramphenicol palmitate having a size of less than 0.5 microns.

Example 3

A mixture of 50.0g of chloramphenicol palmitate and 3.5g of polyoxyethylene (n=20) sorbitan palmitate was melted and then the molten mixture was quenched to 5°C to provide a solid material, which was pulverized by means of a mortar and added to 1 liter of water. By dispersing the aqueous mixture in an attrition type colloid mill, a suspension of fine crystals of chloramphenicol palmitate having a size of less than 0.5 microns was obtained.

Example 4

A mixture of 50.0g of chloramphenicol palmitate and 4.0g of polyoxyethylene (n=20) sorbitan stearate was melted and the molten mixture was added to 1 liter of water cooled to 3—0°C with stirring. After heating the aqueous mixture to 40°C, the mixture was dispersed by means of an attrition type colloid mill to provide a suspension of fine crystals of chloramphenicol palmitate having a size of less than 0.5 microns.

Example 5

A mixture of 60.0g of chloramphenicol palmitate and 2.4g of polyoxyethylene (n=60) hardened castor oil derivative was melted and the molten mixture was added to 1 liter of water cooled to 3—0°C with stirring. After heating the mixture of 40°C, the mixture was dispersed by means of an attrition type colloid mill to provide a suspension of fine crystals of chloramphenicol palmitate having a size of less than 0.5 microns.

Example 6

A mixture of 60.0g of chloramphenicol palmitate and 3.5g of polyoxyethylene (n=20) sorbitan monostearic acid ester was melted and the mixture was quenched to 5°C to provide a solid material, which was pulverized by means of a mortar and was added to 1 liter of water containing 400g of sucrose, 1.52g of p-hydroxybenzoic acid methyl ester, and 5g of sodium carboxy methyl cellulose. By dispersing the resultant mixture by means of an attrition type colloid mill, a suspension of fine crystals of chloramphenicol palmitate having a size of less than 0.5 microns was obtained.

Example 7

A mixture of 60.0g of chloramphenicol palmitate and 2.5g of polyoxyethylene (n=25) stearic acid ester was melted and the molten mixture was added to 1 liter of water containing 300g of sucrose and 5g of sodium carboxy-methyl cellulose cooled to 0—3°C. After heating the resultant mixture to 40°C, the mixture was dispersed by means of an attrition type colloid mill to provide a suspension of fine crystals of chloramphenicol palmitate having a size of less than 0.5 microns.

Example 8

A mixture of 50.0g of chloramphenicol palmitate and 3.0g of polyoxyethylene (n=60) hardened castor oil was melted and the mixture was quenched to 5°C to provide a solid material, which was pulverized by means of a mortar and added to 1 liter of water containing 400g of sucrose. After heating the resultant mixture to 40°C, the mixture was dispersed by means of an attrition type colloid mill to provide a suspension of fine crystals of chloramphenicol palmitate having a size of less than 0.5 microns.

WHAT WE CLAIM IS:—

1. A process for the preparation of a suspension of fine crystals of chloramphenicol palmitate which comprises mix-melting chloramphenicol palmitate and 3—10% by weight based on the chloramphenicol palmitate of at least one nonionic surface active agent selected from polyoxyethylene (n=15—30) higher fatty acid (C_{12}—C_{18}) esters, polyoxyethylene (n=10—25) sorbitan higher fatty acid (C_{12}—C_{18}) esters, polyoxyethylene (n=10—20) polyoxypropylene (m=1—4) higher alcohol (C_{12}—C_{18}) ethers, polyoxyethylene (n=15—30) alkyl (C_8—C_{10}) aryl ethers, and polyoxyethylene (n=50—80) hardened castor oil where n and m are as herein defined, solidifying the molten mixture by quenching it, and dispersing the solidified mixture in an aqueous suspension medium by means of a colloid mill.

2. A process according to claim 1 wherein the aqueous suspension medium is water.

3. A process according to claim 1 wherein the aqueous suspension medium is an aqueous solution of sodium carboxymethyl cellulose.

4. A process according to claim 1 wherein the aqueous suspension medium is an aqueous solution of methyl cellulose.

5. A process according to any of claims 1 to 4 comprising directly adding the molten mixture to a cooled aqueous suspension medium to quench and solidify the molten mixture, and dispersing the mixture by means of a colloid mill.

6. A process according to claim 5 wherein the suspension medium has been cooled to a temperature lower than 5°C.

7. A process according to any of claims 1 to 6 wherein the suspension medium containing the solidified mixture is heated before dispersion by means of the colloid mill.

8. A process for preparing a suspension substantially as hereinbefore described in any one of the Examples.

9. A suspension prepared by a process according to any one of claims 1 to 8.

10. A suspension substantially as hereinbefore described in any one of the Examples.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1973.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.